Review: transfusion-related acute lung injury: pathophysiology, laboratory investigation, and donor management

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Transfusion-related acute lung injury (TRALI) is a serious clinical syndrome that is temporally associated with the transfusion of plasma-containing blood components. The syndrome typically occurs within 6 hours of transfusion. Approximately 80 percent of cases will resolve within 96 hours with supportive care. The syndrome has been associated with antibodies to WBC antigens and generation of biologically active mediators in stored cellular blood components. Appropriate laboratory investigation of TRALI can be crucial in confirmation of the clinical diagnosis, as well as in decisions regarding donor management. ***Immunohematology* 2004;20:103–111.**

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Transfusion-related acute lung injury (TRALI) is a syndrome that is clinically indistinguishable from acute respiratory distress syndrome (ARDS).[1] TRALI can occur within 6 hours of transfusion, but usually occurs within 1 to 2 hours.[2] Symptoms and signs can include shortness of breath, difficulty breathing, hypoxia, fever, hypotension, and hypertension preceding hypotension.[3] All plasma-containing blood components, including whole blood, packed RBCs, fresh frozen plasma,[2] platelet concentrates,[4,5] apheresis platelets,[6,7] granulocytes,[8] cryoprecipitate,[9] allogeneic bone marrow,[10] and IVIG,[11] have been associated with TRALI. Although the pathogenesis of TRALI is not completely understood, it has been associated with antibodies to WBCs[2,7,12] and with the infusion of biologically active mediators in stored cellular blood components.[13,14]

Clinical Syndrome

In most cases of TRALI, clinical symptoms begin within 1 to 2 hours of completion of the transfusion. Symptoms can begin up to 6 hours after transfusion.[2] There are rare case reports of mild symptoms beginning within 6 hours of transfusion with rapid resolution of symptoms and reappearance of more severe symptoms about 24 hours after transfusion.[15] Signs and symptoms include fever, dyspnea, hypotension, hypertension followed by hypotension, and noncardiogenic pulmonary edema. Although any of these signs and symptoms can be seen in TRALI, not all of them will be present in every case.

Patients who are intubated, at the time of the reaction or shortly after the reaction begins, are described as producing copious quantities of frothy fluid from the endotracheal tube.[16–19] The frothy quality of this fluid is secondary to its high protein content. The ratio of protein concentration in edema fluid to protein concentration in the blood in patients with noncardiogenic pulmonary edema is typically > 0.7, while the ratio is usually < 0.5 in cardiogenic pulmonary edema.[20] Yost et al.[21] analyzed the protein content of pulmonary edema fluid in seven cases of TRALI that occurred after liver transplantation. In all seven cases, the ratio of protein in the pulmonary edema fluid to protein in the blood was > 0.7.

The chest X-ray becomes abnormal at the time of the reaction. In recumbent patients, a patchy infiltrate may first appear in the dependent areas of the lungs. The infiltrate rapidly progresses to bilateral "white out." This pattern is caused by pulmonary edema and is indistinguishable from the pattern seen in ARDS.

In approximately 80 percent of cases, the symptoms completely resolve within 96 hours of transfusion.[2] Once the symptoms resolve, there are no chronic manifestations of TRALI. Fatal reactions occur in 5 percent to 10 percent of cases. Fatalities can occur acutely at the time of the reaction or after a protracted

course of mechanical ventilation. In the remaining cases, patients fully recover after intensive support and mechanical ventilation.

Differential diagnosis

The most important factor in the differential diagnosis of TRALI is to determine the nature of the pulmonary edema. The edema in TRALI is noncardiogenic in nature. Other forms of pulmonary edema include cardiogenic and volume overload. TRALI, or noncardiogenic pulmonary edema, can easily be confused with these other two types of pulmonary edema, particularly in critically ill patients and those who have received large volumes of intravenous fluids, including blood components.

Volume overload pulmonary edema is associated with other signs of fluid overload, including jugular venous distension and increased blood pressure. Cardiogenic pulmonary edema is associated with signs and symptoms of heart failure, including gallops, murmurs, or possibly evidence of myocardial ischemia/infarction on electrocardiogram. Additionally, laboratory tests for myocardial infarction and heart failure, including creatine kinase, troponin, and B-type natriuretic peptide, can aid in the differential diagnosis. All of these tests should be within normal limits in TRALI.

Incidence

TRALI is one of the most common causes of transfusion-related mortality. It has been reported as the third leading cause of transfusion-related mortality in the United States[22] and the most common cause in the United Kingdom.[23] An accurate estimate of the incidence of TRALI has been difficult to establish. Most of the published estimates of the incidence of TRALI are based upon calculating the number of cases of TRALI that occur at a specific institution over a period of time, compared to the number of components or patients transfused during the same period. These studies have led to estimates of one case of TRALI per 5000 components transfused[2] and one case per 2400 patients transfused.[24]

Although these studies give an estimate of the incidence of TRALI, there is a growing appreciation that TRALI may be underdiagnosed and underreported.[25] A recent retrospective study examined the medical records of the recipients of blood components donated by a female donor who was implicated in a fatal case of TRALI.[25] The implicated donor had a strong antibody to the granulocyte 5b antigen (HNA-3a) and had donated apheresis plasma (600 mL) in a frequent plasma donation program. The medical records of 36 recipients of this donor's plasma were reviewed by transfusion service medical directors for indications of TRALI associated with transfusion of the blood components. Reactions were classified as mild to moderate or severe. Severe reactions were defined as acute onset of pulmonary edema, or need for mechanical ventilation, associated with transfusion. Mild to moderate reactions were defined as dyspnea, and/or oxygen desaturation without overt clinical evidence of pulmonary edema, associated with transfusion. Eight severe reactions were identified in eight recipients, while seven mild to moderate reactions were identified in six recipients. Only two of the eight severe reactions were reported to the transfusion service, while five of the seven mild to moderate reactions were reported to the transfusion service. Only two of the reactions (one mild to moderate and one severe) were reported to the blood collection facility. The two reactions reported to the blood collection facility were the fatal reaction that prompted the look-back and a mild to moderate reaction that occurred at the same institution during the initial investigation of the fatality. The observation that mild to moderate TRALI reactions were reported to the transfusion service more frequently than severe reactions may be explained by the fact that the mild to moderate manifestations of TRALI can clinically resemble febrile nonhemolytic transfusion reactions (FNHTR) that are routinely reported to the transfusion service.

This "look-back" study emphasizes the importance of clinical recognition of TRALI. Pulmonary symptoms that occur within 6 hours of transfusion should be reported to the transfusion service for further investigation, particularly when there is no other clinical explanation for the symptoms. After investigation by the transfusion service, probable cases of TRALI should be referred to the blood collection facility for donor testing and possible deferral of implicated donors, depending upon the results of the laboratory investigation.

The Antibody Hypothesis for TRALI

The first published case report of what was most likely TRALI was reported in 1951.[26] During the next 30 years there were several case reports of noncardiogenic pulmonary edema associated with transfusion.[8,16,27–34] These case reports attribute the

pulmonary edema to several different causes, including incompatibility of an undetermined nature,[28] human leukocyte antigen (HLA) incompatibility,[32] non-HLA leukoagglutinins,[30] undefined granulocyte leukoagglutinins,[34] and severe allergic pulmonary edema.[8,16,31] Antibodies to HLA Class I and granulocyte antigens were associated with TRALI by Popovsky et al.[2,17] In a series of 36 patients, granulocyte antibodies were identified in the serum of at least one implicated donor in 89 percent of cases. The presence of lymphocyte antibodies was determined, by reverse lymphocytotoxic crossmatch, in the serum of at least one implicated donor, in 26 of the 36 cases (72%). Specificity of the HLA antibodies was further characterized by lymphocyte panel testing in 17 of the 26 cases with HLA antibody. A clear HLA specificity was determined in 11 of the 17 cases (65%). The specificity of the antibody was determined to correspond to at least one of the recipient's HLA antigens in 10 of the 17 cases.

Many of the early case reports of TRALI report the presence of granulocyte or HLA antibodies based upon a positive reverse granulocyte or lymphocyte crossmatch. The results of these tests can be misleading because of the presence of other antigen systems on these cells. This has the potential to result in incorrect interpretation of crossmatch results. An example of this is the granulocyte 5b antigen. Since this antigen is present on lymphocytes in addition to granulocytes,[35,36] a positive reverse lymphocyte crossmatch may lead to the misinterpretation that lymphocyte or HLA antibodies are responsible for the TRALI reaction.

The technologies available to identify HLA antibodies have dramatically evolved in the last 10 years with the availability of solid phase assays such as flow cytometry and ELISA in most histocompatibility laboratories. Because these technologies are based upon isolation and adherence of HLA antigens to a latex bead (flow cytometry) or solid surface (ELISA), they are more specific for detection of HLA antibodies than tests based upon lymphocytotoxicity. Additionally, these tests do not depend upon the ability of the antibody to activate complement and cause cellular lysis.

A recent study by Kopko et al.[7] investigated 16 cases of TRALI. This study examined donor-recipient pairs involved in TRALI reactions. Donors were tested for HLA and monocyte antibodies by flow cytometry, HLA antibodies via a lymphocytotoxic panel, and granulocyte antibodies by granulocyte agglutination (GA) and granulocyte immunofluorescence (GIF). Recipients were typed for HLA Class I and II antigens in all cases. If the donor(s) did not possess HLA or granulocyte antibodies, the recipient was evaluated for antibodies to HLA Class I and II antigens. In 14 of the 16 cases (87.5%), a correlation was identified between antibody present in the donor or the recipient and antigen in the other member of the donor-recipient pair. The identity of the antibody involved in these cases was HLA Class I (4), HLA Class II (5), HLA Class I and II (2), granulocyte (1), and monocyte (2). In the two cases where antibody was not identified, recipient samples were not available for antibody testing. Several recent case reports support the association of HLA Class II antibodies with TRALI.[12,37–40]

Six of the 16 TRALI cases described above were further investigated for the ability of the sera containing antibody from one member of the donor-recipient pair to activate monocytes in the other member of the pair. The fraction of cells expressing the cytokines interleukin 1β (IL-1β) and tumor necrosis factor α (TNF-α) or tissue factor were measured as an indicator of monocyte activation. Expression of the two cytokines and tissue factor were measured after exposure to autologous serum, control serum (serum from the donor of another blood component the patient received or ABO-matched control serum), or serum involved in the TRALI reaction. There was significantly increased expression of all three factors in the monocytes exposed to TRALI serum compared to autologous serum and control serum ($p < 0.05$).

TRALI has been reproduced in an ex vivo animal lung model.[41] In this model, pulmonary edema is produced after a latent period of 3 to 6 hours when rabbit lungs are perfused with 5b-positive granulocytes, antibody to granulocyte 5b, and rabbit plasma as a source of complement. If any of these three components is absent, pulmonary edema does not occur. The pulmonary edema produced in these experiments was noncardiogenic in nature. This was demonstrated by monitoring of pulmonary artery pressure, which displayed only a transient and moderate increase. Increased pulmonary vascular permeability was the cause of the edema.

In the antibody-mediated model of TRALI, antibody-coated leukocytes localize to the pulmonary microvasculature. Cytokine release by these leukocytes is thought to damage the vascular endothelium. Damage to the endothelium of the pulmonary microvasculature is thought to cause increased vascular permeability. This results in leakage of protein-rich fluid into the

pulmonary alveoli and results in pulmonary edema. This theory is supported by the findings of McCullough et al.,[42] who have demonstrated that ^{111}Indium-labeled granulocytes localize to the pulmonary microvasculature when transfused to a recipient with antibodies directed against the granulocytes.

A recent case report suggests that interaction of antibody with leukocytes may not be necessary for TRALI to occur.[43] In this case, a 34-year-old woman who received two units of packed RBCs approximately 10 weeks after undergoing a lung transplant experienced a TRALI reaction. Pulmonary edema was present in the transplanted, but not in the native, lung. Antibodies to HLA-B[44] were identified in the donor of the second unit of packed RBCs. No leukocyte antibodies were identified in the donor of the first unit of packed RBCs. The transplanted lung possessed the HLA-B antigen, while the patient did not. Since very few WBCs of donor origin would be expected to be present in the transplant recipient 10 weeks after transplant, and the pulmonary endothelial cells would be expected to be of donor origin, this case suggests that TRALI may be initiated directly through antibody interaction with endothelial cells.

The Biologically Active Mediator Model for TRALI

Biologically active mediators in cellular blood components, at or near the time of outdate, have been associated with TRALI.[13] In this theory of TRALI, biologically active mediators or lipids accumulate during storage of cellular blood products, including packed RBCs and platelets. These agents enhance or prime neutrophil NADPH Oxidase. In this model, two events are required for a reaction to occur.[44] In the first event, biologically active mediators are generated during physiologic stress. These stressors can include events such as trauma, infection, recent surgery, and massive transfusion. Generation of biologically active compounds, related to stress, is hypothesized to activate the pulmonary vascular endothelium and prime neutrophils. These actions are thought to cause sequestration of neutrophils within the pulmonary microvasculature. The second event consists of the infusion of biologically active mediators in a cellular blood component.

This model of TRALI is supported by a retrospective study performed by Silliman and colleagues.[14] The records of ten transfusion recipients who experienced TRALI were assessed for the presence of a "first event" that would have predisposed them to develop TRALI. A control group of ten patients who experienced a febrile or urticarial reaction was also assessed for the presence of a "first event" prior to transfusion. All of the patients in the TRALI group had an underlying clinical factor that could have predisposed them to develop TRALI, while only two patients in the control group had such underlying clinical factors. Clinical factors thought to predispose a patient to developing TRALI included infection, cytokine administration, recent surgery, and massive transfusion.

This mechanism of TRALI has also been reproduced in an ex vivo animal lung model.[45] In this study, rat lungs were first pretreated with lipopolysaccharide (LPS) to simulate sepsis. The lungs were perfused with one of the following solutions: buffered salt solution, 5% human plasma in saline, 5% supernatant from day 0 or day 5 platelets (both whole blood–derived and apheresis platelets), or lipid extracts from day 0 or day 5 platelets. Pulmonary edema (lung weight) and leukotriene B_4 levels (a measure of lung injury) were measured. Plasma from day 5 apheresis or whole blood–derived platelets, as well as lipid extracts from these components, caused increased pulmonary edema ($p < 0.05$) when the lungs were first treated with LPS compared to saline pretreated and saline perfused lungs. Pulmonary edema did not develop if the lungs were pretreated with saline instead of LPS. Lungs perfused with supernatant or lipid extract from day 0 whole blood–derived or apheresis platelets did not develop pulmonary edema. Leukotriene B_4 levels were increased in the lung perfusate ($p < 0.05$) only after pretreatment with LPS and perfusion of the lungs with 5% supernatant from day 5 platelets. Leukotriene B_4 levels were not measured after treatment with lipid extracts. Prestorage leukoreduction of platelets did not alter the pulmonary edema that developed in these experiments. Pulmonary artery pressure was monitored in these experiments to ensure the edema was noncardiogenic in nature. Significant, sustained increases in pulmonary artery pressure were not observed.

Silliman et al.[46] recently published a study of 90 TRALI reactions occurring during a 4-year period at a single institution. The blood components implicated in these reactions were platelet concentrates (72), apheresis platelets (2), packed RBCs (15), and plasma (1). The first 46 reactions were analyzed in a nested case-control study. Patient and blood component data were compared in these cases to a control group of

225 recipients of platelet concentrates. TRALI was not associated with patient age or gender, incompatibility of patient-donor blood groups, number of previous transfusions, or number and type of previous transfusion reactions. TRALI was associated with a diagnosis of hematologic malignancy ($p < 0.0004$) and cardiac disease ($p < 0.0006$). TRALI was also associated with increasing age of platelet concentrate transfused ($p = 0.014$). Pretransfusion and posttransfusion samples from the last 51 patients who experienced TRALI were analyzed for the accumulation of polymorphonuclear neutrophil leukocyte priming activity. There was significantly more priming activity ($p < 0.05$) in the posttransfusion samples compared to pretransfusion samples and controls.

Pathophysiology of TRALI

Although two seemingly dissimilar mechanisms have been associated with TRALI, it is possible that both mechanisms may be involved in the reaction. Activation of leukocytes with endothelial damage, increased vascular permeability, and resultant pulmonary edema are common to the antibody-mediated model of TRALI and the biologically active mediator model of TRALI. Additionally, look-back studies have shown that the presence of antibody in a donor is not sufficient to cause TRALI in all recipients, even if the recipient possesses an antigen corresponding to the infused antibody.[25,47] These studies suggest that two events may be needed for TRALI to occur. Biologically active mediators have been demonstrated in cellular blood components, while they have not been routinely demonstrated in FFP. Since FFP has frequently been implicated in TRALI,[7,18,31,48] biologically active mediators alone can't explain all cases of TRALI.

An important point to remember when considering the two hypotheses for TRALI is that the differences in transfusion practice around the country and around the world may affect the findings in TRALI investigations. Although the author's institution has reported identifying antibody in one member of the donor-recipient pair in the majority of cases, those data are possibly biased by our area's transfusion practices. Hospitals supplied by the author's blood center have exclusively received apheresis platelets for more than a decade. For the last 7 years, the apheresis platelets have been leukocyte reduced during the collection process. Additionally, the overwhelming majority (> 98%) of RBCs collected within the last few years have been prestorage leukoreduced. Therefore, if biologically active mediators are associated with nonleukoreduced platelet and RBC concentrates,[46] it would be unlikely that a case of TRALI due to these substances would be found at the author's center.

Clinical Investigation

The laboratory investigation of TRALI can be a frustrating and costly task. Cases of TRALI are often referred to the clinical laboratory with a large number of implicated blood components. Additionally, the laboratory is seldom provided data regarding when the implicated blood components were transfused relative to the reaction. Since most cases of TRALI occur within 1 to 2 hours of transfusion, this information is essential to the laboratory investigation of TRALI. Therefore, it is important to obtain this detail prior to initiating testing. This allows the laboratory to prioritize testing of implicated donors. The use of a testing algorithm in the laboratory investigation of TRALI can significantly reduce the cost of working up a case.

It is strongly recommended that donor-recipient pairs be investigated in TRALI cases. One of the most important steps needed to accomplish a complete laboratory investigation is to obtain the appropriate samples from the recipient as soon as TRALI is considered a possibility. If recipient samples for HLA typing and antibody studies are not drawn early in the investigation, they may not be available if they are needed to correlate results in the recipient with results from the donor(s).

A suggested testing algorithm is presented in Table 1. Testing should begin with female donors of blood components transfused within 2 hours of the reaction. Since testing for HLA antibodies is more readily available than testing for granulocyte antibodies, and HLA antibodies have recently been associated with TRALI more often than granulocyte antibodies, testing can begin with HLA Class I and II antibodies. If no HLA antibodies are detected, testing for granulocyte antibodies should be performed. The recipient should be HLA typed (Class I and II) to determine whether antibodies identified in a donor correspond to recipient antigens.

If female donors of blood components transfused within 2 hours of the reaction are negative for HLA and granulocyte antibodies, female donors of blood components transfused within 6 hours of the reaction should be tested for HLA antibodies, followed by testing for granulocyte antibodies. If all female donors

Table 1. Laboratory investigation of TRALI

Recipient samples and testing
1. When TRALI is first suspected, obtain serum/plasma and cellular samples (citrate anticoagulant)
2. Obtain HLA Class I and II typing on cellular samples or freeze cells for DNA for future testing
3. Freeze recipient serum/plasma sample for future testing (prereaction and postreaction samples, if available)
4. Separate and freeze liquid portion of remaining contents of bag, if available, for future testing
Donor testing—HLA and granulocyte
1. Obtain transfusion history including: a. Unit number of transfused component(s) b. Start/stop times of all components transfused c. Time of first symptoms of reaction d. Gender of donor of each of the components transfused within 6 hours of reaction symptoms
2. Test female donors of components transfused within 2 hours of reaction for HLA Class I and II antibodies a. If positive—correlate with recipient HLA typing (donor in step 4) i. If correlation exists—stop b. If negative—test donors (recipient in step 4) for granulocyte antibodies i. If positive—correlate with antigens in recipient (donor in step 4) 1. If correlation exists—stop ii. If negative—proceed to next step
3. Test female donors of components transfused within 6 hours of reaction for HLA Class I and II antibodies (go to step 2a)
4. If recipient is at increased risk of having antibodies (multiparous or recipient of an organ allograft or multiple transfusions) and received a cellular blood component (go to step 2a)
5. Test male donor of components transfused within 2 hours of reaction for HLA Class I and II antibodies (go to step 2a)
6. Test male donors of components transfused within 6 hours of reaction for HLA Class I and II antibodies (go to step 2a)
7. Consider obtaining monocyte antibody testing (available through research laboratories only)
Testing for biologically active mediators
Testing should be considered (available through research laboratories only) if: • Recipient received a cellular blood component with little plasma content • Reaction occurred after transfusion of an autologous blood component

of blood components transfused within 6 hours of the reaction are negative for HLA and granulocyte antibodies, the recipient can be tested for these antibodies. This step will allow diagnosis of the approximately 10 to 15 percent of TRALI cases that are associated with antibodies in the recipient. If the transfusion recipient is at high risk of having leukocyte antibodies, due to a history of pregnancy or transfusion, it may be advisable to test the recipient for antibodies earlier in the course of the workup, particularly if the patient received a nonleukocyte reduced cellular blood component (i.e., packed RBCs or platelets).

If the recipient and the female donors of blood components transfused within 6 hours of the reaction are negative for HLA and granulocyte antibodies, male donors of blood components transfused within 2 hours of the reaction can be tested next. If the testing is still negative, male donors of blood components transfused within 6 hours of the reaction can be tested. At any point in the TRALI investigation, if antibody is identified in one member of the donor-recipient pair and it corresponds to antigen in the other member of the donor-recipient pair, further workup can be halted.

Currently, testing for monocyte antibodies and biologically active mediators is not commercially available. If testing for HLA and granulocyte antibodies is negative in the donor(s) and recipient, testing for these other factors associated with TRALI can be obtained through research laboratories.

Treatment

Because TRALI occurs infrequently, there are no clinical studies of appropriate treatment after a reaction has occurred. The only treatments that can be recommended are supportive care for the patient's symptoms, including oxygen support with or without mechanical ventilation, and fluid administration. The use of steroids for treatment of TRALI is anecdotal. Therefore, no recommendation regarding steroid use can be made.

One caution in the treatment of TRALI is the avoidance of diuretics. There are several case reports that describe worsening of the patient's clinical condition and even fatality following administration of diuretics after a reaction.[8,18] Since the pulmonary edema associated with TRALI is noncardiogenic, patients are not typically volume overloaded. The patient may be hypovolemic due to the underlying condition or secondary to the extravasation of fluid into the lungs. Therefore, administration of diuretics can lead to hypotension, decreased cardiac output, and decreased pulmonary capillary wedge pressure.[8,18]

Donor Management Issues

One of the most important considerations regarding TRALI is donor management. Several different suggestions regarding donor management have been published. These include deferring all females from donating plasma for transfusion,[49]

deferring multiparous females from donating plasma for transfusion,[49] deferring multiparous females from plasma donation unless their serum has been tested for antibodies to leukocytes,[50] and deferring donors implicated in a TRALI case, if they have been found to have antibody in their serum that corresponds to antigen on the TRALI patient's leukocytes.[25,50] Each of these donor management strategies would reduce the risk of TRALI in transfusion recipients. However, none of them would completely eliminate TRALI.

Deferring high-risk donors from donating plasma components would not eliminate the risks associated with the plasma in other blood components. A recent retrospective study correlated the volume of plasma in a blood component with the likelihood that a blood component would be implicated in a TRALI case.[51] If the volume of plasma in a blood component correlates to the risk of TRALI from a blood component, then apheresis platelets would have a slightly greater risk of causing TRALI than plasma derived from a whole–blood donation. None of the deferral strategies that exclude donors based upon gender or parity include deferral from apheresis platelet donation. Additionally, very small volumes of plasma have been shown to cause TRALI.[27] These deferral strategies would not prevent cases of TRALI secondary to the small volumes of plasma present in cryoprecipitate or RBC and platelet concentrates.

None of the donor management strategies would prevent cases of TRALI secondary to antibody in the recipient. Finally, none of the strategies would address the association of TRALI with biologically active lipids.

There are also obstacles to screening female or multiparous donors for antibodies to leukocytes. In order to screen for leukocyte antibodies, a test that could be performed on a large number of donors in a short period of time would be needed. Although screening tests for HLA Class I and II antibodies using flow cytometry or ELISA methodologies are currently available commercially, there are no such tests available for screening for antibodies to the granulocyte 5b antigen. Since this antibody has recently been reported in association with three fatal cases of TRALI,[25,52] inclusion of a test for this antibody in a screening test would be ideal.

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